CLAIMS

What is claimed is:

1. A method of mitigating one or more symptoms associated with chronic consumption of a substance of abuse by a mammal, said method comprising:

administering to said mammal an effective amount of an adenosine receptor antagonist; and

an effective amount of a dopamine receptor antagonist;

wherein the effective amount of the adenosine receptor antagonist is lower than the effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist.

2. The method of claim 1, wherein the effective amount of the dopamine receptor antagonist is lower than the effective amount of a dopamine receptor antagonist administered without said adenosine receptor antagonist.

3. The method of claim 1, wherein the combined dosage of dopamine receptor antagonist and adenosine receptor antagonist is just sufficient to produce minimum activation of PKA in response to consumption of a substance of abuse.

4. The method of claim 1, wherein the dopamine receptor antagonist is administered at a standard therapeutic dosage.

5. The method of claim 1, wherein the dopamine receptor antagonist is administered at about a threshold dosage.

6. The method of claim 1, wherein the dopamine receptor antagonist is administered at a sub-threshold dosage.

7. The method of claim 1, wherein the adenosine receptor antagonist is administered at a standard therapeutic dosage.

8. The method of claim 1, wherein the adenosine receptor antagonist is administered at about a threshold dosage.

9. The method of claim 1, wherein the adenosine receptor antagonist is administered at a sub-threshold dosage.

10. The method of claim 1, wherein said substance of abuse is selected from the group consisting of an opioid, a barbiturate, a cannabinoid, cocaine, an amphetamine, alcohol, and nicotine.

11. The method of claim 1, wherein said dopamine receptor antagonist is selected from the group consisting of butaclamol, chlorpromazine, domperidone, fluphenazine, haloperidol, heteroaryl piperidines, metoclopramide, olanzapine, perospirone hydrochloride hydrate, phenothiazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, and zotepine.

12. The method of claim 1, wherein the effective dosage of the dopamine receptor antagonist is low enough to avoid causing an adverse symptom characteristically produced by administration of a dopamine receptor antagonist.

13. The method of claim 12, where said adverse symptom is selected from the group consisting of tardive dyskensia, dystonia, and neuroendocrine (hormonal) disturbances.

14. The method of claim 1, wherein said adenosine receptor antagonist is selected from the group consisting of PD115,199; ZM 241385, quinazoline, 3-(3-hydroxyphenyl)-5H-thiazolo[2,3b]-guinazoline, 1,3-diethyl-8-phenylxanthine, and other substituted phenylxanthines.

15. The method of claim 1, wherein the effective dosage of the adenosine receptor antagonist is low enough to avoid causing an adverse symptom characteristically produced by administration of an adenosine receptor antagonist.

16. The method of claim 15, where said adverse symptom is selected from the group consisting of sleep disorders, elevated heart rate, and arrhythmia.

17. The method of claim 1, wherein the dopamine receptor antagonist and the adenosine receptor antagonist are administered sequentially.

18. The method of claim 1, wherein the dopamine receptor antagonist and the adenosine receptor antagonist are administered simultaneously.

19. The method of claim 1, wherein the dopamine receptor antagonist and the adenosine receptor antagonist are administered in a single unit dosage formulation.

20. The method of claim 1, wherein said symptom is a chronic consumptive behavior.

21. A composition comprising an effective amount of an adenosine receptor antagonist; and an effective amount of a dopamine receptor antagonist, wherein the effective amount of the adenosine receptor antagonist is lower than the effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist.

22. The composition of claim 21, wherein the effective amount of the dopamine receptor antagonist is lower than the effective amount of a dopamine receptor antagonist administered without said adenosine receptor antagonist.

23. The composition of claim 21, wherein the combined dosage of dopamine receptor antagonist and adenosine receptor antagonist is just sufficient to inhibit activation of PKA in response to consumption of a substance of abuse.

24. The composition of claim 21, wherein the dopamine receptor antagonist is at a standard therapeutic dosage.

25. The composition of claim 21, wherein the dopamine receptor antagonist is at about a threshold dosage.

26. The composition of claim 21, wherein the dopamine receptor antagonist is at a sub-threshold dosage.

27. The composition of claim 21, wherein the adenosine receptor antagonist dosage at a standard therapeutic dosage.

28. The composition of claim 21, wherein the adenosine receptor antagonist is at about a threshold dosage.

29. The composition of claim 21, wherein the adenosine receptor antagonist is at a sub-threshold dosage.

30. The composition of claim 21, wherein said dopamine receptor antagonist is selected from the group consisting of butaclamol, chlorpromazine, domperidone, fluphenazine, haloperidol, heteroaryl piperidines, metoclopramide, olanzapine, perospirone hydrochloride hydrate, phenothiazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, and zotepine.

31. The composition of claim 21, wherein the effective dosage of the dopamine receptor antagonist is low enough to avoid causing an adverse symptom characteristically produced by administration of a dopamine receptor antagonist.

32. The composition of claim 31, where said adverse symptom is selected from the group consisting of tardive dyskensia, dystonia, and neuroendocrine (hormonal) disturbances.

33. The composition of claim 21, wherein said adenosine receptor antagonist is selected from the group consisting of f PD115,199; ZM 241385, quinazoline, 3-(3-hydroxyphenyl)-5H-thiazolo[2,3b]-guinazoline, 1,3-diethyl-8-phenylxanthine, and other substituted phenylxanthines.

34. The composition of claim 21, wherein the effective dosage of the adenosine receptor antagonist is low enough to avoid causing an adverse symptom characteristically produced by administration of an adenosine receptor antagonist.

35. The composition of claim 21, wherein the dopamine receptor antagonist and the adenosine receptor antagonist in a single unit dosage formulation.

36. A method of mitigating one or more symptoms associated with withdrawal associated with cessation of consumption of a substance of abuse by a mammal, said method comprising:

administering to said mammal an effective amount of an adenosine receptor agonist; and

an effective amount of a dopamine receptor agonist;

wherein the effective amount of the adenosine receptor agonist is lower than the effective amount of an adenosine receptor agonist administered without said dopamine receptor agonist.

37. The method of claim 36, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is sufficient to maintain changes in gene expression associated with chronic consumption of a substance of abuse.

38. The method of claim 36, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is just sufficient to activate a PKA pathway.

39. The method of claim 36, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is sufficient to reduce a symptom of withdrawal from a substance of abuse.

40. The method of claim 36, wherein the effective amount of the dopamine receptor agonist is lower than the effective amount of a dopamine receptor agonist administered without said adenosine receptor agonist.

41. The method of claim 36, wherein the dopamine receptor agonist is administered at a standard therapeutic dosage.

42. The method of claim 36, wherein the dopamine receptor agonist is administered at about a threshold dosage.

43. The method of claim 36, wherein the dopamine receptor agonist is administered at a sub-threshold dosage.

44. The method of claim 36 wherein the adenosine receptor agonist is administered at a standard therapeutic dosage.

45. The method of claim 36, wherein the adenosine receptor agonist is administered at about a threshold dosage.

46. The method of claim 36, wherein the adenosine receptor agonist is administered at a sub-threshold dosage.

47. The method of claim 36, wherein said substance of abuse is selected from the group consisting of an opioid, a barbiturate, cocaine, an amphetamine, a cannabinoid, alcohol, and nicotine.

48. The method of claim 36, wherein said dopamine receptor agonist is selected from the group consisting of Bromocriptine, CY 208-243, SKF 83959 , ABT-431, SKF 38393, SKF 81297, LY 171555, R(-)-10, and 11-dihydroxy-N-n-propylnorapomorphine (NPA).

49. The method of claim 36, wherein the effective dosage of the dopamine receptor agonist is low enough to avoid causing an adverse symptom characteristically produced by administration of a dopamine receptor agonist.

50. The method of claim 49, where said adverse symptom is orthostatic hypotension.

51. The method of claim 36, wherein said adenosine receptor agonist is selected from the group consisting of. CGS21680 (Ciba-Geigy), 2-phenylaminoadenosine (CV1808), N,6-cyclohexyl-adenosine, and N,6-cyclopentyladenosine.

52. The method of claim 36, wherein the effective dosage of the adenosine receptor agonist is low enough to avoid causing an adverse symptom characteristically produced by administration of an adenosine receptor agonist.

53. The method of claim 52, where said adverse symptom is selected from the group consisting of drowsiness, inability to concentrate, uncoordination, and sedation,

54. The method of claim 36, wherein the dopamine receptor agonist and the adenosine receptor agonist are administered sequentially.

55. The method of claim 36, wherein the dopamine receptor agonist and the adenosine receptor agonist are administered simultaneously.

56. The method of claim 36, wherein the dopamine receptor agonist and the adenosine receptor agonist are administered in a single unit dosage formulation.

57. The method of claim 36, wherein said symptom is selected from the group consisting of craving for a substance of abuse, delerium tremens, irritability, frustration, anger or anxiety, difficulty in concentrating, restlessness, increased appetite, insomnia, depression, seizures, and relapse.

58. A composition for mitigating a symptom of withdrawal from a drug of abuse, said composition comprising an effective amount of an adenosine receptor agonist; and an effective amount of a dopamine receptor agonist, wherein the effective amount of the adenosine receptor agonist is lower than the effective amount of an adenosine receptor agonist administered without said dopamine receptor agonist.

59. The composition of claim 58, wherein the effective amount of the dopamine receptor agonist is lower than the effective amount of a dopamine receptor agonist administered without said adenosine receptor agonist.

60. The composition of claim 58, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is sufficient to maintain changes in gene expression associated with chronic consumption of a substance of abuse.

61. The composition of claim 58, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is just sufficient to activate a PKA pathway.

62. The composition of claim 58, wherein the combined amount of dopamine receptor agonist and adenosine receptor agonist is sufficient to reduce a symptom of withdrawal from a substance of abuse.

63. The composition of claim 58, wherein the dopamine receptor agonist is in a dosage range that is a standard therapeutic dosage.

64. The composition of claim 58, wherein the dopamine receptor agonist is at about a threshold dosage.

65. The composition of claim 58, wherein the dopamine receptor agonist is a sub-threshold dosage.

66. The composition of claim 58, wherein the adenosine receptor agonist is a dosage range that is a standard therapeutic dosage.

67. The composition of claim 58, wherein the adenosine receptor agonist is at about a threshold dosage.

68. The composition of claim 58, wherein the adenosine receptor agonist is a sub-threshold dosage.

69. The composition of claim 58, wherein said substance of abuse is selected from the group consisting of an opioid, a barbiturate, a cannabinoid, cocaine, an amphetamine, alcohol, and nicotine.

70. The composition of claim 58, wherein said dopamine receptor agonist is selected from the group consisting of Bromocriptine, CY 208-243, SKF 83959 , ABT-431, SKF 38393, SKF 81297, LY 171555, R(-)-10, and 11-dihydroxy-N-n-propylnorapomorphine (NPA).

71. The composition of claim 58, wherein the effective dosage of the dopamine receptor agonist is low enough to avoid causing an adverse symptom characteristically produced by administration of a dopamine receptor agonist.

72. The composition of claim 71, where said adverse symptom is orthostatic hypotension.

73. The composition of claim 58, wherein said adenosine receptor agonist is selected from the group consisting of. CGS21680 (Ciba-Geigy), 2-phenylaminoadenosine (CV1808), N,6-cyclohexyl-adenosine, and N,6-cyclopentyladenosine.

74. The composition of claim 58, wherein the effective dosage of the adenosine receptor agonist is low enough to avoid or reduce an adverse symptom characteristically produced by administration of an adenosine receptor agonist.

75. The composition of claim 74, where said adverse symptom is selected from the group consisting of drowsiness, inability to concentrate, uncoordination, and sedation,

76. The composition of claim 58, wherein the dopamine receptor agonist and the adenosine receptor agonist comprise a single unit dosage formulation.

77. The composition of claim 58, wherein said symptom is selected from the group consisting of craving for a substance of abuse, delerium tremens, irritability, frustration, anger or anxiety, difficulty in concentrating, restlessness, increased appetite, insomnia, depression, relapse, and seizure.

78. A method of mitigating one or more symptoms associated with chronic consumption of a substance of abuse by a mammal, said method comprising inhibiting expression or activity of a beta/gamma dimer.

79. The method of claim 78, wherein said substance of abuse is alcohol.

80. The method of claim 78, wherein the symptom is consumptive behavior.

81. The method of claim 78, wherein said inhibiting expression or activity comprises contacting said beta/gamma dimer with a moiety that specifically binds to said beta/gamma dimer.

82. The method of claim 81, wherein said beta/gamma dimer is a beta-1/gamma 2 dimer.

83. The method of claim 81, wherein said moiety is a beta/gamma dimer scavenger peptide.

84. The method of claim 81, wherein said moiety is a beta/gamma dimer specific antibody.

85. The method of claim 81, wherein said moiety is a beta/gamma dimer specific intrabody.

86. A method of mitigating consumptive behavior or craving after withdrawal of a substance of abuse, said method comprising:

administering to a mammal an agent that increases effective adenosine levels or activity of an adenosine receptor in a concentration sufficient to mitigate said consumptive behavior or craving.

87. The method of claim 86, wherein said agent is an agent that inhibits adenosine reuptake.

88. The method of claim 86, wherein said agent is dipyrrimidole.

89. The method of claim 86, wherein said agent is an adenosine receptor agonist.

90. The method of claim 86, wherein said agent is selected from the group consisting of PD115,199; ZM 241385, quinazoline, 3-(3-hydroxyphenyl)-5H-thiazolo[2,3b]-guinazoline, 1,3-diethyl-8-phenylxanthine, and other substituted phenylxanthines.

91. The method of claim 86, wherein said agent is an adenosine deaminase inhibitor or an adenosine kinase inhibitor.

92. The method of claim 86, wherein said agent is selected from the group consisting of erythro-9[2-hydroxyl-3-nonyl] adenine (EHNA), 2'-deoxycoformycin (DCF), 2'-deoxycoformin, 5'amino-5'-deoxyadenosine, 5'-deoxy-5-iodotubercidin, 5'-iodotubericidin, iodotubericidin (16), iodotubericidin, GP515 (17), 4-(N-phenylamino)-5-phenyl-7-(5'-deoxyribofuranosyl)pyrrolo[2,3-d]pyrimidi ne (GP683).

93. A method of mitigating consumptive behavior or craving during chronic consumption of a substance of abuse, said method comprising:

administering to a mammal engaging in said chronic consumption of a substance of abuse, an adenosine receptor antagonist in a concentration sufficient to mitigate said consumptive behavior or craving.

94. The method of claim 93 wherein said adenosine receptor antagonist is selected from the group consisting of PD115,199; ZM 241385, quinazoline, 3-(3-hydroxyphenyl)-5H-thiazolo[2,3b]-guinazoline, 1,3-diethyl-8-phenylxanthine, and other substituted phenylxanthines.

95. A method of screening for an agent that modulates the effect of a substance of abuse on PKA activation in a mammalian cell, said method comprising:

contacting a mammalian test cell with a test agent; and

detecting the expression or activity of a beta/gamma dimer of said test cell wherein a difference in beta/gamma dimer expression or activity in said test cell as compared to beta/gamma dimer expression or activity in a control cell indicates that said test agent modulates the effect of a substance of abuse on PKA activation.

96. The method of claim 95, wherein said beta/gamma dimer is a beta-1/gamma-2 dimer.

97. The method of claim 95, wherein a decrease in the expression or activity of a beta/gamma dimmer indicates that said test agent decreases the activation of PKA associated with said substance of abuse.

98. The method of claim 95, wherein said substance of abuse is selected from the group consisting of alcohol, an opiate, a barbituate, a cannabinoid, and nicotine.

99. The method of claim 95, wherein said method further comprises contacting said test cell with said substance of abuse.

100. The method of claim 95, wherein an adenosine receptor pathway in said test cell is activated.

101. The method of claim 95, wherein said test cell comprises αS.

102. The method of claim 95, wherein said test cell comprises PKCα.

103. The method of claim 95, wherein said test cell is cultured ex vivo.

104. The method of claim 95, wherein said test agent is administered to a non-human mammal.

105. The method of claim 95, wherein said control cell is a positive control contacted with said test agent at a higher concentration than said test cell.

106. The method of claim 95, wherein said control cell is a negative control contacted with said test agent at a lower concentration than said test cell.

107. The method of claim 106, wherein said control cell is not contacted with said test agent.

108. The method of claim 95, wherein said test cell is a nerve cell.

109. The method of claim 95, wherein the expression of a beta/gamma dimer is detected by detecting a mRNA encoding a polypeptide that comprises a beta/gamma dimer.

110. The method of claim 109, wherein the level of said mRNA is measured by hybridizing said mRNA to a probe that specifically hybridizes to a nucleic acid tat encodes a polypeptide that comprises a beta/gamma dimer.

111. The method of claim 110, wherein said hybridizing is according to a method selected from the group consisting of a Northern blot, a Southern blot using DNA derived from the RNA encoding a polypeptide comprising a beta/gamma dimer, an array hybridization, an affinity chromatography, and an *in situ* hybridization.

112. The method of claim 110, wherein said probe is a member of a plurality of probes that forms an array of probes.

113. The method of claim 109, wherein the level of mRNA encoding a polypeptide that comprises a beta/gamma dimer is measured using a nucleic acid amplification reaction.

114. The method of claim 95, wherein the expression or activity of a beta/gamma dimer is detected by detecting the level of a beta/gamma dimer in said cell.

115. The method of claim 114, wherein said detecting is via a method selected from the group consisting of capillary electrophoresis, a Western blot, mass spectroscopy, ELISA, immunochromatography, and immunohistochemistry.

116. The method of claim 95, wherein the expression or activity of a beta/gamma dimer is detected by detecting activity of a PCA pathway.

117. The method of claim 116, wherein said activity is detected by detecting translocation of a component of a PKA pathway.

118. A method of screening for an agent that decouples dopamine receptor activity from an adenosine receptor pathway, said method comprising:

contacting a test cell comprising a dopamine receptor with a test agent;

detecting the expression or activity of a beta-gamma dimer wherein a decrease in beta/gamma dimer expression or activity in said cell as compared to beta/gamma dimer expression or activity in a control cell indicates that said test agent decouples dopamine receptor activity from an adenosine receptor pathway

119. A method of prescreening for an agent that modulates the effect of a substance of abuse on PKA activation in a mammalian cell, said method comprising:

i) contacting a beta/gamma dimmer or a nucleic acid that encodes a polypeptide comprising a beta/gamma dimmer with a test agent; and

ii) detecting specific binding of said test agent to a beta/gamma dimmer or to a nucleic acid that encodes a polypeptide comprising a beta/gamma dimer wherein specific binding indicates that said agent is a candidate agent modulates the effect of a substance of abuse on PKA activation in a mammalian cell.

120. The method of claim 119, further comprising recording test agents that specifically bind to a beta/gamma dimmer or to a nucleic acid that encodes a polypeptide comprising a beta/gamma dimer in a database of candidate agents that modulates the effect of a substance of abuse on PKA activation in a mammalian cell.

121. The method of claim 119, wherein said test agent is not an antibody.

122. The method of claim 119, wherein said test agent is a beta/gamma scavenger peptide.

123. The method of claim 119, wherein said test agent is not a protein.

124. The method of claim 119, wherein said test agent is not a nucleic acid.

125. The method of claim 119, wherein said test agent is a small organic molecule.

126. The method of claim 119, wherein said detecting comprises detecting specific binding of said test agent to a nucleic acid that encodes a polypeptide comprising a beta/gamma dimer.

127. The method of claim 126, wherein said binding is detected using a method selected from the group consisting of a Northern blot, a Southern blot using DNA derived from the

RNA encoding a polypeptide comprising a beta/gamma dimer, an array hybridization, an affinity chromatography, and an *in situ* hybridization.

128. The method of claim 119, wherein said detecting comprises detecting specific binding of said test agent to a beta/gamma dimer.

129. The method of claim 128, wherein said detecting is via a method selected from the group consisting of capillary electrophoresis, a Western blot, mass spectroscopy, ELISA, immunochromatography, and immunohistochemistry.

130. The method of claim 119, wherein said test agent is contacted directly to the a beta/gamma dimmer or to a nucleic acid that encodes a polypeptide comprising a beta/gamma dimer.

131. The method of claim 119, wherein said test agent is contacted to a mammalian cell.

132. The method of claim 131, wherein said cell is cultured *ex vivo*.

133. The method of claim 119, wherein said test agent is administered to a non-human mammal.

134. A composition comprising an adenosine receptor antagonist and a dopamine receptor antagonist in a pharmacologically acceptable excipient.

135. The composition of claim 134, wherein the combination of an adenosine receptor antagonist and dopamine receptor antagonist are sufficient to mitigate a symptom associated with chronic consumption of ethanol.

136. The composition of claim 134, wherein said composition comprises a unit dosage formulation.

137. A kit comprising:
a container containing an adenosine receptor antagonist; and
a container containing a dopamine receptor antagonist.

138. The kit of claim 137, wherein said container containing an adenosine receptor antagonist; and said a container containing a dopamine receptor antagonist are the same container.

139. The kit of claim 137, wherein said adenosine receptor antagonist is in a pharmacologically acceptable excipient.

140. The kit of claim 137, wherein said dopamine receptor antagonist is in a pharmacologically acceptable excipient.

141. The kit of claim 137, further comprising instructional materials teaching the use of a combination of an adenosine receptor antagonist and a dopamine receptor antagonist to mitigate a symptom associated with chronic consumption of a substance of abuse.

142. A composition comprising an adenosine receptor agonist and a dopamine receptor agonist in a pharmacologically acceptable excipient.

143. The composition of claim 142, wherein the combination of an adenosine receptor agonist and dopamine receptor agonist are sufficient to mitigate a symptom associated with withdrawal from chronic consumption of ethanol.

144. The composition of claim 142, wherein said composition comprises a unit dosage formulation.

145. A kit comprising:
a container containing an adenosine receptor agonist; and
a container containing a dopamine receptor agonist.

146. The kit of claim 145, wherein said container containing an adenosine receptor agonist; and said a container containing a dopamine receptor agonist are the same container.

147. The kit of claim 145, wherein said adenosine receptor agonist is in a pharmacologically acceptable excipient.

148. The kit of claim 145, wherein said dopamine receptor agonist is in a pharmacologically acceptable excipient.

149. The kit of claim 145, further comprising instructional materials teaching the use of a combination of an adenosine receptor agonist and a dopamine receptor agonist to mitigate a symptom associated with withdrawal from chronic consumption of a substance of abuse.